European Journal of Human Genetics (2014) 22, 3–5
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www.nature.com/ejhg

VIEWPOINT

Return of whole-genome sequencing results in paediatric research: a statement of the P3G international paediatrics platform

This article has been corrected since Advance Online Publication and a corrigendum also appears in this issue

Bartha Maria Knoppers*,[1], Denise Avard[1], Karine Sénécal[1] and Ma'n H Zawati[1] along with the P3G International Paediatrics Platform members[2]

European Journal of Human Genetics (2014) **22,** 3–5; doi:10.1038/ejhg.2013.176; published online 7 August 2013

Keywords: Paediatric research; whole-genome sequencing; best interests of the child

Whole-genome sequencing (WGS) reveals the genome of an individual including both rare mutations and genes that have a role in the expression of common medical conditions. The rapid development of WGS has substantially reduced both the cost and the time required to sequence an entire human genome. The availability of WGS is likely to change the current practice of both paediatric medicine and research by facilitating more accurate, sophisticated and cost-effective genetic testing.[1] WGS also reveals findings with clinical significance that are not within the scope of the original paediatric research objectives. This raises the ethical question of whether to return such WGS findings.

Our purpose in this statement is to examine how to respect the 'best interests of the child' – 'a primary consideration'[2] – as well as the right of the child to voice his or her opinion[3] in the particular context of paediatric research using WGS. In the text below, we will use the term WGS results to include both research results *per se* (ie within the objectives of the project) and 'incidental' findings that are revealed via WGS. Our background reflections cover both existing and emerging guidance, approaches for the testing of adults, and relevant laws, before we propose our recommendations.

EXISTING GUIDANCE

General criteria

At a general level, publically accessible lay summaries of general research results for research participants are increasingly the norm. More specifically, when the research project involves young children, these general results should be offered to the parents or guardians. When the research project involves adolescents, general results should also be offered to them in a manner appropriate to their level of development, comprehension and maturity.

Communication of all individual WGS results, however, including those revealing possible adult predisposition or those of uncertain clinical significance, could lead to the over-prescribing of tests and create undue parental anxiety. There are also potential psychological harms such as alteration of self-image, distortion of parental perception of the child, increased anxiety and guilt, familial stress related to the identification of other at-risk family members, difficulty obtaining life and/or disability insurance, and the detection of non-paternity.[4,5] Yet, WGS may well reveal scientifically validated results with clinical utility that are medically actionable during childhood and thus would benefit the individual child. In all situations, and taking the specific context into account, the child's best interests should guide decision making.[6]

The release of WGS information is also complicated by the fact that children mature as they grow older and thus become more autonomous in their decision-making abilities. The mechanism for recognizing this in the research context is requiring assent from the child according to the degree and level of his or her maturity.[7] This is how the child can be involved and engaged in the decision-making process.[8,9]

Generally, professional guidance on the communication of genetic information has favoured waiting until the child is capable of understanding its nature and consequences, including familial consequences. Accordingly, at maturity, a child could decide to undergo genetic testing or not. But today, with the arrival of WGS, we are faced with the issues of which WGS results should be communicated (or not) before the child reaches the age of majority as well as the familial consequences.

Specific criteria

The 2005 European *Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research*[10] states that a condition for undertaking research with a child unable to consent is that 'the results of the research have the potential to produce real and direct benefit to his or her health…[unless]…the ultimate attainment of results…[confers] benefit…to other persons in the same age category or afflicted with the same disease or disorder' (art. 15). The latter 'benefit to others' serves as an exemption to the direct benefit requirement. Nevertheless, even if the research meets the 'benefit to others' requirement, it still must present only a minimal risk and a minimal burden to the child participant. This is important because the *Additional Protocol* targets clinical research, where as in the genetic research context, the nature of the risks and burdens are different.

Indeed, for genetic testing for health purposes, it is instructive to note that this accepted research exemption to the direct benefit criterion is absent. Article 10 of the

[1]Centre of Genomics and Policy, McGill University, Montreal, Quebec, Canada
[2]See appendix for a list of the members.
*Correspondence: Professor BM Knoppers, Department of Human Genetics, McGill University, 740, avenue Dr Penfield, suite 5200, Montreal, Quebec, Canada H3A 0G1. Tel: +514 398 8155; Fax: +514 398 8954; E-mail: bartha.knoppers@mcgill.ca

2008 *Additional Protocol Concerning Genetic Testing for Health Purposes*[11] mandates that 'a genetic test on a person who does not have the capacity to consent may only be carried out for his or her direct benefit…[and] where, according to law, a minor does not have the capacity to consent, a genetic test on this person shall be deferred until attainment of such capacity unless that delay would be detrimental to his or her health or well-being.'

Further, consistent with the recognition of both the familial nature of genetic testing and the possible needs of family members, this same Protocol also states that 'exceptionally, and by derogation from the provisions of…article 10…the law may allow a genetic test to be carried out, for the benefit of family members, on a person who does not have the capacity to consent, if some specific conditions are met…[they include tests]…to allow the family member(s) concerned to obtain a preventive, diagnostic or therapeutic benefit that has been independently evaluated as important for their health…[and if] the expected benefit has been independently evaluated as substantially outweighing the risk for private life that may arise from the collection, processing or communication of the results of the test' (art. 13). This position recognizes the notion of familial interests as a consideration in determining the child's best interests.

More recently, the European Society of Human Genetics (ESHG) published its *Principles for Good Practice in Paediatric Biobanks*,[12] which provided guidance on the return of results to minors in the specific context of biobanks. The Principles stated that '[t]he right of parents to receive or not receive genetic information about their children is limited.'[4,5] But, '[i]n the rare case that information about a preventable or treatable early-onset disease is found, [parents] should be notified regardless of their wishes provided the findings are subject to assessment of clinical validity and utility.'[6]

At the national level, the 2010 British Society for Human Genetics *Report on the Testing of Children*, making no distinction between the research and clinical contexts, recommended against both predictive and presymptomatic genetic testing. '[I]n such circumstances testing should normally be delayed until the young person can decide for him/herself when, or whether to be tested.'[13] Similarly, the 2012 Canadian *Best Practices for Research Involving Children and Adolescents: Genetic, Pharmaceutical, and Longitudinal Studies*[14] maintained that 'individual research results and incidental findings should be communicated (1) if they are scientifically valid, (2) if they have significant implications for the health of the child or adolescent, and (3) if a treatment or method of prevention is available during childhood or adolescence' (chapter 8).

EMERGING GUIDANCE

In 2013, both the American Academy of Pediatrics and the American College of Medical Genetics and Genomics provided both a *Policy Statement on the Ethical and Policy Issues in Genetic Testing and Screening of Children*[4,5] and a *Technical Report: Ethical and Policy Issues in Genetic Testing and Screening of Children*.[5] This *Policy Statement*, as well as the *Technical Report*, reaffirmed that decisions about offering genetic testing and screening should be driven by the best interests of the child. It went on to support the traditional professional recommendations to defer genetic testing for late-onset conditions until adulthood.

Yet, the *Technical Report* also stipulated that 'predictive genetic testing may be appropriate in limited circumstances…. In deciding whether a child should undergo predictive genetic testing for late-onset conditions, the focus must be on the child's medical best interests; however, parents and guardians may also consider the potential psychosocial benefits and harms to the child and the extended family.' Thus, it conceded '[e]xtending consideration beyond the child's medical best interest…recogniz[ing] that the interest of a child is embedded in and dependent on the interests of the family unit.' It concluded that '[a]fter careful genetic counselling, it may be ethically acceptable to proceed with predictive genetic testing to resolve disabling parental anxiety or to support life-planning decisions that parents sincerely believe to be in the child's best interest.'

This recognition of the possible legitimacy of familial and reproductive interests thus broadened the narrow 'paediatric-actionability' criterion. Not long thereafter, however, the American College of Medical Genetics and Genomics adopted a more radical and controversial position. It mandated obligatory testing of a panel of 57 reportable genetic conditions by laboratories undertaking WGS irrespective of whether adults or children are involved or of any personal parental choice other than to not have the indicated test at all.[15,16]

Additionally, some authors have also suggested that paediatric researchers have a 'limited responsibility' to disclose certain genomic research findings.[17] This includes findings 'of genetic variants with known, urgent clinical significance' for the child. The criteria for what constitutes 'urgent clinical significance' include clear and direct benefit for the child and that the benefit outweighs the potential risks for psychological and social harm.

Other considerations include the fact that '[r]esearchers already have been able to help clinicians aid some children born with rare birth defects by sequencing and analysing their whole genomes to diagnose and treat their illnesses.' Such 'medical' sequencing, while justified for treatment purposes, still raises concerns 'with regard to fully informed decision making' since 'whole-genome sequence data obtained from a minor already could have been widely shared before the minor reached an age at which they could determine preferred data sharing limits themselves, thereby decreasing their autonomy.'[18] Further, the emergence of paediatric longitudinal biobank studies further complicates the WGS issues surrounding the return of results as asymptomatic children may be enrolled at birth.[19]

APPROACHES FROM ADULT TESTING

As WGS enters both paediatric research and even clinical practice for children with rare disorders, some lessons can also be drawn from the use of WGS in research involving adults. A number of approaches have sought to limit the amount of unsolicited information revealed. First, filters can restrict testing by the laboratory to only the research results actually sought. Second, binning regroups results into categories based on scientific validity, clinical utility, and actionability. A third approach uses an independent, multidisciplinary clinical oversight committee to act in an advisory capacity. However, all three are complicated in paediatric research by the exercise of parental authority and choice over health decisions concerning their children.[20]

RELEVANT LAWS

Finally, although not specific to genetic information, a recent overview of laws and policies underscored the lack of guidelines specific to the paediatric research context.[21] The authors identified a number of issues that need to be included: more transparency on the return of general research results; the need to distinguish between therapeutic (actionable) results and those that are of unknown clinical significance; the need to consider the specific condition and context of the study; and the mode, timing and delivery of validated research results.

To this, we could add the need to inform parents of any policy concerning future recontact (or not), as well as the possibility of communicating a change of interpretation of any results or findings during childhood.

It is against this international background on research and genetic testing involving children that the recommendations of the P3G Paediatric Platform on the communication of WGS should be situated.

RECOMMENDATIONS

We propose the following recommendations for sharing WGS results as being in the best interests of the child:

1. The issue of the possible return (or not) of WGS results should be discussed during the informed consent process.
2. During the consent/assent process, the child's or adolescent's views should be solicited and given due weight and consideration in accordance with his or her age and maturity.
3. WGS results that are scientifically valid, clinically useful, and reveal conditions that are preventable and actionable during childhood should be offered.
4. Mutations that predispose the child to develop an adult-onset disorder, even if accidentally discovered in the research process, generally should not be returned. This allows the child to make his or her own decision about receiving the results as an adult.
5. Questions, which should arise rarely, of whether the child would benefit, on balance, from disclosure because of the potential benefit to the family from knowing about a highly penetrant gene they may have that poses serious risk to health and that is preventable or treatable, should be assessed on a case-by-case basis.

This is a cautious approach and WGS may well become routine one day, perhaps even at birth. We have avoided defining scientific terms such as 'validity', 'utility' or 'prevention' believing them to be the purview of professional societies and scientific analysis. The aim is to not only provide a flexible approach for practice but also to recognize the need for clinical judgment[22] as concerns both WGS and future advances. When countries begin to introduce WGS as a routine paediatric diagnostic tool for more precise and earlier diagnosis and treatment, both the duties of researchers and the standard of care will be clarified. Till then, vulnerable children should not be caught up in the current web of uncertainty surrounding the return of WGS results.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

This work was supported by grants from the Canadian Institutes of Health Research and the Terry Fox Foundation (TFF-105266), Genome Canada and the Canadian Institutes of Health Research, Finding of Rare Disease Genes in Canada (FORGE), the Maternal Infant and Youth Research Network (MICYRN), the Network of Applied Genetic Medicine of Québec (RMGA) and the Fonds de recherche en santé du Québec (FRSQ).

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APPENDIX

Annelien L Bredenoord[1], Alison Hall[2], Kristien Hens[3], Wim Pinxten[4], Susan Wallace[5], David Parry[6], Ellen Wright Clayton[7]

[1]Division Julius Center, Medical Humanities, UMC Utrecht; [2]PHG Foundation, Cambridge, UK; [3]Department of Health, Ethics and Society, Maastricht University; [4]Department of Medical Ethics and Philosophy of Medicine, Erasmus, MC; [5]Department of Health Sciences, University of Leicester; [6]Centre of Genomics and Policy, McGill University; [7]Vanderbilt University Law School.